Evaluation and Treatment of Men with Biochemical Prostate-Specific Antigen Recurrence Following Definitive Therapy for Clinically Localized Prostate Cancer

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Early detection and monitoring by serum prostate-specific antigen (PSA) measurement has increased the number of men presenting with potentially curable prostate cancer. Most will choose radical prostatectomy or some form of radiation therapy for treatment, but some will have evidence of biochemical disease recurrence following therapy, shown by a rising PSA level without other clinical evidence of disease. Radical prostatectomy involves the removal of all prostate tissue, causing the serum PSA to decline to undetectable levels within four to six weeks following surgery; a subsequent rise in the serum PSA to a detectable level indicates disease recurrence. Patients should be evaluated to assess whether rising PSA levels indicate local recurrence or early metastatic disease. The advantages of salvage radiation, endocrine therapy, and other treatment modalities in local disease recurrence must be weighed against potential side effects and the resulting decrease in quality of life. Radiation therapy does not immediately eradicate all PSA-producing cells; therefore the persistence of a detectable PSA does not necessarily imply residual cancer, but rising PSA levels indicate treatment failure. Salvage surgery can be performed after radiotherapy for the purpose of removing all viable cancer cells, but should be weighed against a higher incidence of surgical complications; cryoablation offers a less invasive therapeutic modality.
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Key words: Prostate-specific antigen • Gleason score • External beam radiation • Transrectal ultrasound • Immunoscintigraphy • Cryoablation

Prostate cancer is now the most common noncutaneous malignancy in American men, with an estimated 179,300 new cases diagnosed in the United States in 1999.[1,2] The measurement of serum prostate-specific antigen (PSA) for early detection and monitoring of men with prostate cancer as well as heightened public and professional awareness has dramatically increased the

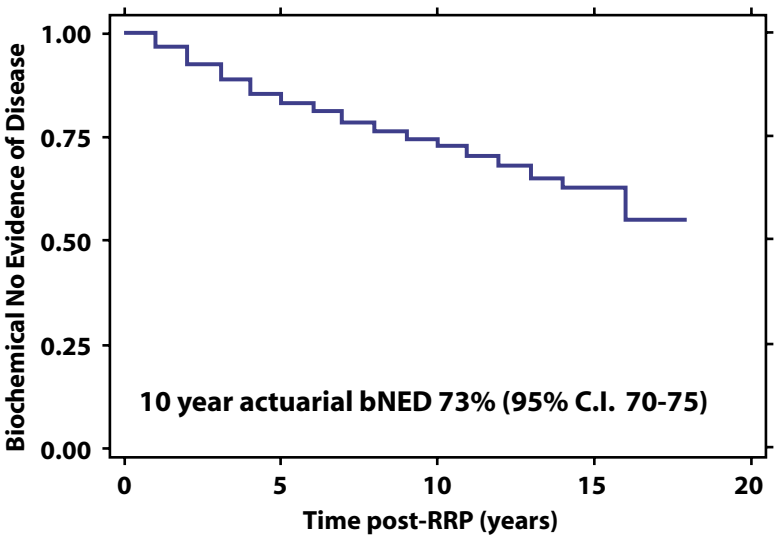


Figure 1. *Actuarial biochemical PSA with no evidence of disease (bNED) for 2,600 men treated with radical retropubic prostatectomy (RRP) only by Patrick C. Walsh, MD (The Johns Hopkins Hospital) between 1982 and 1999. The 10-year actuarial bNED for this group of men was 73% (95% C.I. of 70-75%).*

number of men presenting with potentially curable disease.[3] While these men with clinically localized disease are faced with a number of different treatment options, the majority will choose either radical prostatectomy or some form of radiation therapy as definitive therapy.[3]

These therapies offer excellent long-term cure rates in men with localized disease, but 30% to 50% of men will have evidence of biochemical PSA disease recurrence at ten years following treatment by either form of therapy (Figure 1). Disease recurrence most often presents in the form of a biochemical recurrence with an isolated, detectable, rising PSA level without other clinical evidence of disease. This review will address the evaluation and treatment options for those men with PSA recurrence after surgical or external beam radiation therapy. Because of the lack of long-term data in the evaluation of men who have undergone interstitial radiation therapy (brachytherapy), only external beam radiation therapy will be included in this discussion.

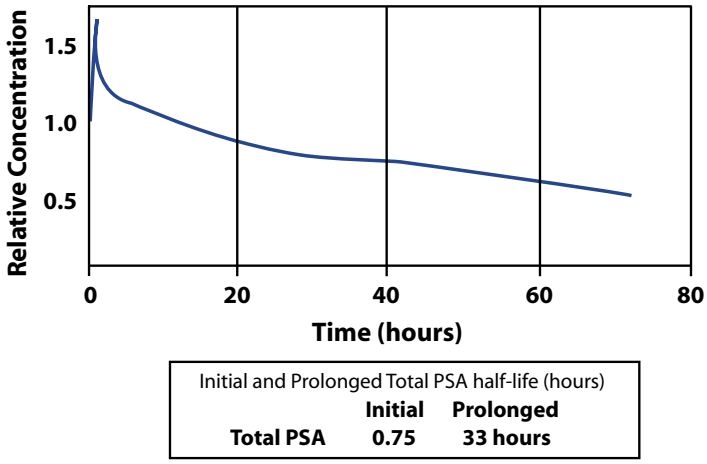


Figure 2. *Kinetics of elimination of total PSA following radical retropubic prostatectomy. Each time point represents the average of ten measurements. Two-phase elimination kinetic model is represented. Initial phase (0.75 hours) follows an immediate rise resulting from surgical manipulation. The prolonged phase has a half-life of 33 hours. All values express a relative concentration normalized to the initial value.*

Radical Prostatectomy

The primary goal of radical prostatectomy is the removal of the entire prostate gland and a surrounding layer of uninvolved tissue. With the removal of all prostate tissue, the serum PSA should rapidly decline to undetectable levels. The kinetics of the elimination of PSA after radical prostatectomy have been reported (Figure 2).[4] The end result of PSA clearance should be an undetectable PSA level within 4 to 6 weeks following surgery. For this reason, the measurement of serial PSA values in postprostatectomy patients serves as an effective means of monitoring for disease recurrence. Although there are isolated reports of local or distant recurrence in the setting of an undetectable serum PSA, disease progression is most often heralded by a rise in the serum PSA to a detectable level.[5-10] Most clinicians recommend initial testing beginning at 3 months, although an undetectable nadir may be reached a few weeks prior to this point in men with low preoperative PSA values. Serial testing is generally performed quarterly during the first year, then biannually or annually unless there is further clinical or laboratory evidence of disease recurrence.[11]

Using an undetectable PSA as an indicator of disease-free status, many larger centers have reported the long-term results of radical prostatectomy for the treatment of localized prostate cancer. The demographics and clinical and pathological stages in these series are demonstrated in Table 1. In the most recent report of the Johns Hopkins series, a 10-year biochemical progression-free rate of 68% was

Table1
Biochemical Recurrence-Free Likelihood of Several Major Radical Retropubic Prostatectomy Series

Author	No. of Men	Mean Age (yr)	Follow-up (mos) Mean (range)	10-Year Biochemical Recurrence-Free Likelihood
Catalona[81]	925	63.7	28 (0-123)	65%
Pound[12]	1623	59.6	60.4 (12-56)	68%
Ohori[82]	500	63	36 (1-110)	73%
Trapasso[83]	601	65	34 (12–237)	47%
Zincke[84]	3170	65.4	60	52%

Modified from Pound CP, Partin AW, Epstein JI, and Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy: Patterns of recurrence and cancer control. *Urol Clin N Amer.* 1997;24(2):395-406.

achieved.[12] These results compare favorably with those seen in other series. A recent update of the Baylor series included an additional 11 months of mean follow-up since the previous report with a relatively stable 10-year progression-free rate of 71%.[13] The progression-free rates in these series reflect 10-year cancer-specific survival rates of 98% in the Baylor series and 15-year cancer-specific survival rates of 91% in the Hopkins series.

Due to the sensitivity of PSA as an indicator of recurrent disease, the time between biochemical recurrence and the onset of clinical disease is variable and somewhat unpredictable. A report of an early prostatectomy series suggested that this period between biochemical and clinical recurrence could range between 6 and 48 months.[14] In the Hopkins series of men with PSA recurrence followed expectantly without adjuvant hormonal therapy, the mean time of progression to metastatic disease was almost 8 years from the time of initial PSA recurrence.[15] The dilemma facing both the clinician and patient during this period is determining whether this rising PSA represents a local recurrence or early metastatic disease. Although factors such as preoperative PSA level, clinical and pathological stage, and prostatectomy Gleason score and time of PSA detection may prove useful in making this prediction, a clinical evaluation of the patient with an isolated PSA recurrence is warranted.

Patient evaluation. The digital rectal examination (DRE) should be the initial method of evaluation for possible local recurrence in men with a PSA recurrence. Local recurrence has been documented in 3% to 23% of men with stage T2 disease or less.[16,17] The role of transrectal ultrasound (TRUS)-guided biopsy in men with biochemical recurrence after radical prostatectomy is controversial. TRUS and biopsy can be helpful in documenting the site of recurrence in some cases. But, although TRUS may increase the sensitivity of the DRE alone, it is marked by a low specificity for local recurrence, with positive and negative predictive values of only 67% and 70%, respectively.[16]

This low specificity stems from the fact that most local recurrences are in the form of multiple, discrete nests of cells, as opposed to a single nodule, making them harder to detect and sample during TRUS-guided biopsy. The postoperative PSA level and pathologic stage of the prostatectomy specimen have been shown to be significant determinants of the likelihood of a positive vesicourethral anastomosis biopsy. In 45 post-radical prostatectomy patients with a 53% positive biopsy rate, no patient with organ-confined disease and a PSA level less than 1.0 ng/mL had a positive biopsy.[18]

Proponents of TRUS and biopsy in patients with biochemical recurrence state that by withholding the use of adjuvant radiation in those men with a negative biopsy, the potential morbidity of incontinence, impotence, strictures, fistulas, and radiation cystitis is avoided. The argument against TRUS biopsy in the setting of a biochemical recurrence is that a negative biopsy

does not provide adequate assurance that a local recurrence does not exist; likewise, a positive anastomotic biopsy does not ensure an isolated local recurrence, because synchronous local and distant recurrences are common. For this reason, some clinicians do not require biopsy-proven evidence of local recurrence before recommending adjuvant radiation therapy. Patients with an isolated biochemical recurrence without radiographic evidence of metastatic disease as well as clinical and pathological parameters consistent with local failure (see below) are assumed to have local recurrence and are offered adjuvant radiation therapy. This approach avoids any potential morbidity from the biopsy itself. Also, the delay in initiation of radiation therapy seen in men undergoing multiple repeat biopsies is eliminated.

A radionuclide bone scan should be performed to evaluate for metastatic disease in the setting of PSA recurrence following surgery. The timing of a radionuclide bone scan in men with a detectable PSA is controversial. The report by Oesterling and colleagues provides indirect evidence that radionuclide bone scintigraphy may not be cost-effective in men with minimal elevations in postoperative PSA levels.[19] They demonstrated that the incidence of a positive bone scan before surgery in men with a PSA of less than 20 ng/mL was only 5%. This issue was directly addressed in a report by Cher and associates, which demonstrated that the probability of a positive bone radionuclide scan was 5% or lower until the serum PSA reached a level of at least 30 to 40 ng/mL.[20] Even with this small likelihood of a positive finding, many clinicians feel that early radionuclide bone imaging studies are useful as a baseline for comparison with future studies that are performed as the PSA ultimately continues to increase. At our institution, radionuclide bone scans are generally obtained at the time of initial biochemical recurrence and then at yearly intervals thereafter, unless symptoms or clinical findings suggest a need for more frequent evaluation. Any suspicious areas on bone scan are verified with plain radiographs. In addition, chest radiographs are also obtained to evaluate for soft-tissue lung metastases.

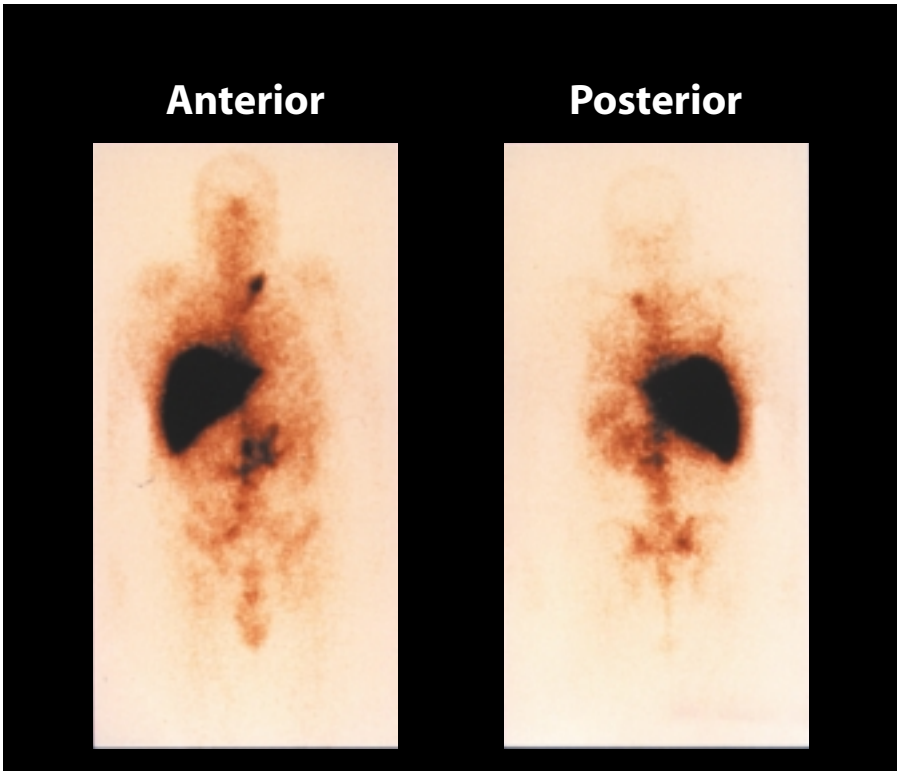


Figure 3. *Immunoscintigraphic (^{111}Indium (In)-capromide pendetide) scanning. Image represents para-aortic and left clavicular evidence of systemic recurrence of prostate cancer following radical prostatectomy in a man with an isolated biochemical recurrence. Large shaded area represents accumulation of radiotracer in the liver. (Images provided by Dr. Michael Haseman).*

Axial imaging is most useful in men felt to have local recurrence who are being considered for salvage therapy. Although computed tomography (CT) has a low sensitivity (60%) for identifying local recurrence within the prostatic fossa, high-resolution scanners may have accuracy rates as high as 93% in detecting metastatic lymph nodes.[21,22] This would prevent the unnecessary use of salvage pelvic radiation therapy in these men who would be better served by systemic therapy. Magnetic resonance imaging (MRI) is felt to be comparable to CT in its ability to detect metastatic lymph nodes, and thus either CT or MRI may be useful in evaluation of a man with suspected local recurrence who is being considered for salvage radiation therapy.[23] MRI may also be useful in evaluating for suspected bony metastases or spinal cord compression when other modalities are inconclusive.[24,25]

Immunoscintigraphy is now being utilized in the evaluation of men with biochemical recurrence after radical prostatectomy (Figure 3). ^{111}Indium (In)-capromab pendetide is a radio-labeled isotope directed towards a prostate-specific membrane antigen that is more highly expressed

in malignant than non-malignant prostate tissue and in metastatic versus primary cancer cells.[26] Most importantly, use of this modality to select men without evidence of extraprostatic spread after radical prostatectomy has resulted in improved success rates for salvage radiotherapy.[27] Although initial reports using this modality are promising, some men with a recurrent PSA predicted to have distant disease based upon the Prostascint scan have not had these findings verified with other radiographic or histologic studies. However, for the most part this new imaging technique has been accurate in targeting the site of recurrence to influence treatment decisions following surgery.[27]

Early reports of the use of positron emission tomography (PET) for the evaluation of lymph node metastases in men with PSA recurrence suggest that PET may even be superior to immunoscintigraphy, but these studies are preliminary.[28] Only with long-term follow-up will the clinical utility of either immunoscintigraphy or PET be verified.

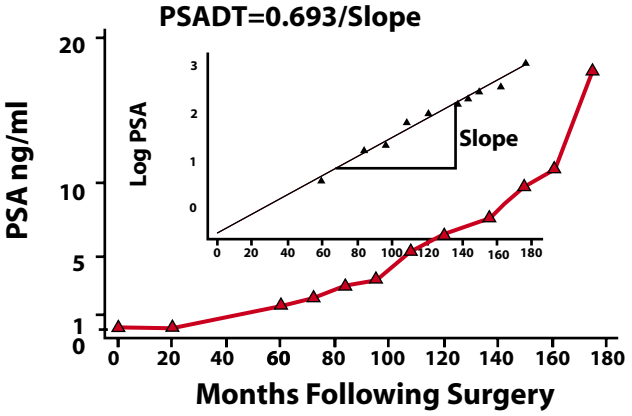


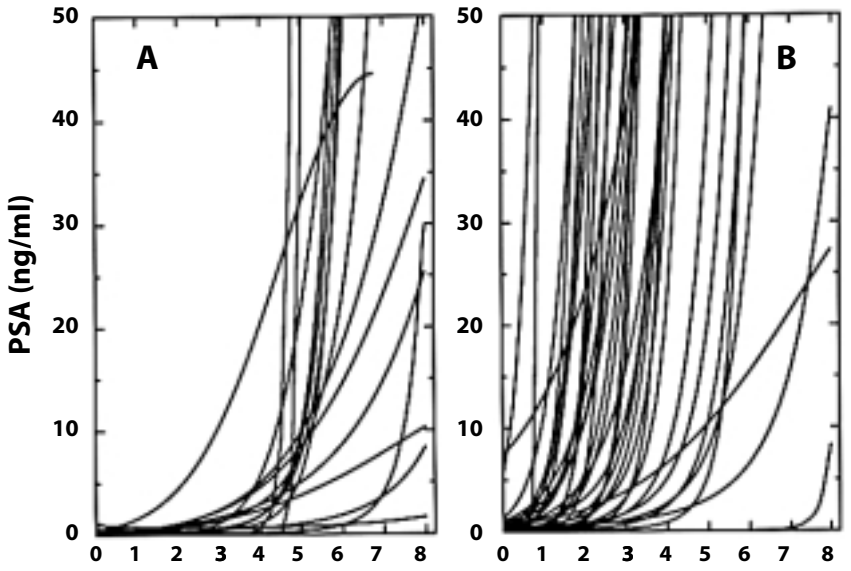
Figure 5. *PSA doubling time (PSADT) is calculated by taking the log (natural log) of the actual PSA levels which provides a straight line (insert). The slope of this log-transformed PSA curve is then used to calculate the PSADT=(ln 2 [0.639]/slope).*

Determination of local versus distant recurrence. Presently there is no method to predict accurately for an individual patient with an isolated PSA recurrence whether he has a local recurrence or distant metastases. Investigators have looked at factors including pathologic indicators, molecular markers, and PSA kinetics in an effort to predict which men would benefit from local treatment strategies while avoiding unnecessary interventions in men destined to fail from metastatic disease.

Partin and colleagues reported that the PSA velocity 1 year after surgery could be used to distinguish local versus distant disease but found that a combination of pathologic stage, Gleason score, and PSA velocity 1 year after surgery best distinguished local recurrence from distant metastases (Figure 4).[29] In particular, men with Gleason scores of 8 or greater and/or involvement of seminal vesicles or lymph nodes on final pathologic analysis had a 95%, 86%, and 100%, respectively, likelihood of failing from metastatic cancer. Cadeddu reported that in 82 men treated with radiation therapy for isolated PSA recurrence, men with these same pathologic criteria (Gleason scores of 8 or greater and positive seminal vesicles or lymph nodes) or a PSA recurrence within 1 year of surgery rarely benefit from radiation therapy.[30]

Danella and associates were the first to suggest the importance of PSA doubling time (PSADT; see Figure 5) in distinguishing metastatic disease from an isolated PSA or local recurrence. More recently, PSADT has been suggested by Patel

Figure 4. *Mixed effects regression estimates of PSA changes after biochemical recurrence following radical prostatectomy for individual men with either local (A) or distant (B) disease. Time to detectable PSA level and rate of change (velocity) are different between local and distant disease recurrences. (Data modified from Partin AW, Pearson JD, Landis PK, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology. 1994;43:649, with permission from authors).*



and colleagues as a useful predictor of type of eventual recurrence after radical prostatectomy.[31] They measured the PSADT for a group of 77 men with biochemical recurrence following radical prostatectomy and found that shorter PSADT's (less than 6 months) were more indicative of distant disease when compared to local recurrence. The PSADT (more than 10 months versus less than 10 months) was also a useful predictor of the probability of development of metastatic disease in a large series of men with isolated PSA recurrence followed without early adjuvant hormonal therapy.[15] In this report, Gleason score as well as the timing of the initial PSA recurrence (less than 2 years or greater than or equal to 2 years following surgery) were also important in determining a man's probability of progressing to distant metastases after the development of biochemical recurrence.

Adjuvant therapy. *Radiation.* Salvage radiation therapy can be successful in selected men with isolated PSA recurrences who lack objective evidence of metastatic disease. Reported success rates at various time intervals vary widely and are in the range of 20% to 59%.[30,32-36] This wide range of reported success is most likely due to patient selection and surgical technique, as well as varying and often vague definitions of clinical success following adjuvant radiation. The long-term results of adjuvant radiation therapy are even more discouraging, with a recent report of only a 10% likelihood of a sustained undetectable PSA (less than 0.2 ng/mL) at 5 years following adjuvant therapy.[30] This series included only men who had initially achieved an undetectable PSA after surgery.

This same criteria for failure was used by Nudell and associates when they reported a 43% 5-year progression-free rate in a series of 105 patients.[36] Thirty-six (34%) of these men received adjuvant radiation therapy immediately after surgery, based on pathologic factors, mainly positive margins, without a documented biochemical recurrence. This progression-free rate may have been artificially elevated in that it has been shown that many patients with positive margins may remain free of disease without adjuvant therapy.[37,38]

An important finding in the study by Nudell and associates was that men with a recurrent PSA level of less than 1.0 ng/mL fared as well as the group of men undergoing salvage radiotherapy prior to a documented biochemical recurrence. This suggests that the delay of adjuvant therapy until the patient has a detectable PSA does not jeopardize any potential benefit from salvage radiation.

The American Society for Therapeutic Radiology and Oncology Consensus Panel recently published guidelines for the role of salvage radiotherapy in men after radical prostatectomy. Panel members also felt that the level of PSA at the time of salvage radiotherapy did have prognostic significance and stated that a PSA level of 1.5 ng/mL is most likely the threshold level for optimal success rates.[39]

Failure after adjuvant radiation therapy is more likely in those men with advanced pathologic stage (Gleason score of more than 7 and seminal vesicle or lymph node involvement).[30] Other factors that have been correlated with a high likelihood of failure include a PSA that does not reach an undetectable level after surgery, an early initial PSA recurrence, or a PSA doubling time of less than 6 months.[33,35,40] Preliminary reports of the use of transient androgen deprivation around the time of salvage radiation therapy have shown improvement in both biochemical and clinical response rates.[41] The use of this regimen is still under clinical investigation at this time and, as stated by the American Society for Therapeutic Radiology and Oncology Consensus Panel, should be used only in a controlled experimental setting.[39]

In counseling men regarding the use of salvage radiotherapy after radical prostatectomy, one should keep in mind the potential risks of this therapy, including GI symptomatology, new or worsened urinary incontinence, and erectile dysfunction. It is best to avoid exposing men with a low likelihood of benefit to these potential risks.

Endocrine therapy. Endocrine therapy can be used to palliate either local or distant recurrence. Unfortunately, its success is not long-standing and is associated with some disadvantages, including cost.[42] Early endocrine therapy in men with prostate cancer is controversial. Some studies have demonstrated a delay in disease progression, but this therapy has not been reliably shown to prolong survival.[43,44]

In counseling men regarding the use of salvage radiotherapy after radical prostatectomy, one should keep in mind the potential risks of this therapy.

Therefore, many clinicians feel that observation with delayed hormonal therapy for either symptomatic or metastatic disease is a valid option for men with an isolated PSA recurrence after surgery. The algorithm provided in the report by Pound and associates provides an estimate of a man's likelihood of remaining free of metastatic disease without adjuvant hormonal therapy for 3, 5, and 7 years following an

initial PSA recurrence.[15] Delayed hormonal therapy is most appropriate in those men not at risk of rapid progression to metastatic disease. This will avoid the high cost of therapy in these men as well as potential side effects and the resulting decrease in their quality of life. The option of delayed therapy may not be as attractive to men with higher risk of impending disease progression. This issue of adjuvant hormonal therapy is being further addressed in an ongoing EORTC trial comparing immediate versus delayed hormonal therapy in men with biochemical recurrence after definitive local therapy.

If one does decide to offer early endocrine therapy, the optimal form of therapy has not been definitely determined. In a recent trial involving men with metastatic prostate cancer, no difference in survival rates was demonstrated in men treated with castration in combination with an antiandrogen.[45] Intermittent hormonal therapy offers the advantage of reduced cost and side effects, but long-term efficacy has yet to be determined. A multicenter, prospective, randomized trial in Europe is ongoing (RELAPSE study) to study this issue further. At this time, use of intermittent androgen ablation in this setting is best suited for controlled clinical trials.[46,47]

The use of androgen receptor blockers and 5α-reductase inhibitors has been studied in an attempt to find an effective form of hormonal therapy with fewer side effects. Finasteride was shown to delay PSA progression in men with biochemical recurrence after radical prostatectomy, but the effect on overall disease progression and survival is not known.[48] Finasteride combined with flutamide may also reduce the PSA level in men with biochemical recurrence after definitive therapy, and the combination of these agents seems to have an additive effect.[49-51] Although these agents seem to be better tolerated than LHRH agonists, with or without an antiandrogen, the long-term effect on disease progression and survival is not known.

Newer treatment modalities. There are several new oral agents that are possible candidates for use as adjuvant therapy in men with biochemical recurrence after definitive therapy. Phenylbutyrate, an analogue of phenylalanine, is a differentiating agent and an inducer of apoptosis in cancer cells. Angiogenesis inhibitors such as thalidomide and anti-inflammatory agents that inhibit COX-2 are being evaluated as potential therapies as well.[52]

One of the most exciting prospects for future therapy in men with recurrent disease involves the use of gene therapy. Many centers around the country are investigating different approaches to this type of therapy. Although these studies are initially focusing on safety and efficacy in men with advanced disease, the ultimate goal will be to find an effective therapy that can be used at an early point of failure of conventional primary therapies.

One of the most exciting prospects for future therapy in men with recurrent disease involves the use of gene therapy.

Radical Prostatectomy: Conclusions and Recommendations

When faced with an initial detectable PSA after radical prostatectomy, repeat evaluation of serum PSA is warranted to rule out laboratory error. If, on repeat testing, the serum PSA remains in the detectable range, our initial evaluation would consist of a thorough history and digital rectal examination. We do not routinely perform biopsy of the vesicourethral anastomosis due to both the lack of beneficial information obtained and the potential morbidity of the procedure itself.

In men felt to be at risk for distant recurrence based on either pathologic features or PSA kinetics, a radiographic evaluation for early signs of metastatic disease is warranted. Although there is a low probability of finding significant disease in men with PSA levels under 10 ng/mL, we feel that these studies function as an initial baseline study with which to compare subsequent studies. These studies are then repeated on an annual basis in the asymptomatic patient or earlier if there are signs or symptoms suggestive of distant disease. Unless the patient is being considered for possible adjuvant local therapy, cross-sectional imaging of the abdomen and/or pelvis is not routinely performed.

Although somewhat controversial, we do not routinely recommend the initiation of hormonal therapy until there is documented clinical evidence of distant metastases. Without more clear evidence of a survival benefit, we feel that the side effects and expense of the early use of therapy outweigh any potential benefit. For similar reasons, we do not provide complete androgen ablation with an antiandrogen except during the first month of therapy in men unwilling to accept delayed hormonal therapy.

In men with a clinical course consistent with local recurrence, we do not require a histologic diagnosis of local recurrence to recommend adjuvant local therapy. A more thorough evaluation of the pelvis and regional

Table 2
Biochemical Recurrence-Free Likelihood of Several Major External Beam Radiation Series

Author	No. of Men	Definition of Biochemical Recurrence	5-year Biochemical Recurrence-Free Likelihood	10-year Biochemical Recurrence-Free Likelihood
Schellhammer[85]	311	>0.5 ng/mL	30%	6%
Kuban[86]	652	4 ng/mL	35%	13%
Zagars[87]	707	2 or more consecutive rising PSA or a second value higher than its predecessor by 1 ng/mL or factor of 1.5	66%	
Lee[88]	364	>1.5 ng/mL or 2 consecutive PSA elevations	56%	
Crook[89]	207	PSA2 ng/mL and 1 ng/mL above previous value	82%*	
Hanks[90]	456	2 consecutive increases in PSA that equals or exceeds 1.5 ng/mL	61%	

*3-year data
Modified from Letran JL and Brawer MK. Management of radiation failure for localized prostate cancer. *Prostate Cancer and Prostatic Diseases* 1998;1:119-127.

lymph nodes is obtained using CT or MRI. It is here that one may consider newer imaging modalities such as Prostascint or PET scans to verify the absence of distant disease before recommending adjuvant local therapy. A radionuclide bone scan and chest x-ray should also be performed as routine studies for metastatic evaluation. Salvage external beam radiation therapy is most effective if administered before the PSA rises above 1.0 to 1.5 ng/mL and is best performed in centers that have a large experience with this technique. While the majority of patients at our institution do undergo neoadjuvant hormonal ablation around the time of

Table 3
Summary of the American Society for Therapeutic Radiology and Oncology Consensus Panel Statement: Guidelines for PSA following Radiation Therapy

- No definition for PSA recurrence is intended to replace evidence of clinical progression or survival.
- PSA nadir is a strong prognostic factor, however, no absolute cut point can be ascribed to predicting success of treatment.
- PSA levels should be obtained at 3- to 4-month intervals for two years following treatment, then every six months thereafter.
- Biochemical failure is not justification to initiate additional therapy, yet represents an appropriate early end point for clinical trials.
- Biochemical failure is defined as three consecutive increases in PSA after radiation treatment.
- For clinical trials, the date of failure should be the midpoint between the postirradiation nadir PSA and the first of the three consecutive rises in PSA.

American Society for Therapeutic Radiology and Oncology Consensus Panel Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiation Oncology Biol Phys.* 1997;37:1035-1041.

the salvage therapy, this is best reserved for controlled experimental settings at this time.

Radiation Therapy

Radiation therapy as treatment for localized prostate cancer can be administered through external beam or interstitial seed implantation (brachytherapy). Due to the popularity of these methods, an increasing number of men are presenting with an isolated biochemical recurrence after these therapies. Because of the lack of long-term data in the evaluation of men who have undergone brachytherapy, only external beam radiation therapy will be discussed here.

One of the major difficulties in the discussion of response rates following radiotherapy is the definition of biochemical recurrence. Unlike radical prostatectomy, radiation therapy does not immediately eradicate all PSA-producing cells; therefore the persistence of a detectable PSA does not necessarily infer the persistence of residual cancer. The average half-life of serum PSA is 1.9 months following radiotherapy, and patients may take up to 18 to 24 months to achieve a nadir value.[53,54]

The consensus statement of the American Society of Therapeutic Radiology and Oncology defined treatment failure after radiotherapy as three consecutive increases in PSA independent of the nadir value (Table 2).[55] This nadir level is an important predictor of response to therapy. A nadir of less than or equal to 0.5 mg/mL has been associated with 5-year recurrence-free rates of above 90%, whereas men with a nadir of 0.6 to 1.0 ng/mL had only a 26% chance of remaining free of disease at 5 years following therapy.[56]

Recently, Kestin and colleagues demonstrated that men with a nadir at or below 0.4 ng/mL who required 2 years or less to reach this nadir had the highest likelihood of long-term cure.[57] Based on these studies, men with nadir values above 0.5 ng/mL are at increased risk of recurrent disease. Table 3 demonstrates the results of several of the larger radiation series. One must bear in mind that lack of consistency in definitions of biochemical recurrence between series will complicate direct comparisons between individual series as well as with radical prostatectomy series.

Patient evaluation. Although the consensus statement from the American Society of Therapeutic Radiology and Oncology advises that routine prostate rebiopsy is not necessary in the standard care of post-radiation therapy patients, men with a rising PSA who are potential candidates for salvage therapy should undergo a prostate rebiopsy. The pathologic analysis of these biopsies after previous radiation therapy can be confusing due to the presence of radiation atypia in the benign prostate glands, which could potentially lead to a false-positive biopsy result.[58] Immunohistochemical techniques using basal cell-specific cytokeratin monoclonal antibodies have been shown to be useful in differentiating benign glands from cancerous ones.[59,60]

As is the case after radical prostatectomy, these men should be evaluated for the presence of metastatic disease with a chest radiograph and a radionuclide bone scan. Evaluation for local extension of disease as well as pelvic or abdominal adenopathy can be performed using either CT or MRI. Cystoscopy should be per-

Table 4
Impact of Preoperative Prognostic Factors (Ploidy, Gleason Histological Score, and Preoperative PSA) on Biochemical PSA Recurrence of Men Undergoing Salvage Prostatectomy following Radiation Failure

Prognostic Factor	10-Year Actuarial PSA Progression-Free Probability (%)
Gleason Score 2-7	55%
Gleason Score 8-10	38%*
Diploid	89%
Tetraploid	50%
Aneuploid	17%**
Preoperative PSA < 10 ng/mL (5-year data)	70%
Preoperative PSA ≥ 10 ng/mL (5-year data)	47%***

* $P<.05$
** $P<.001$
*** $P=.057$

Amling CL, Lerner SE, Martin SK, et al. Deoxyribonucleic acid ploidy and serum prostate-specific antigen predict outcome following salvage prostatectomy for radiation refractory prostate cancer. *J Urol.* 1999;161:857. Mayo Clinic 1999 with permission.

formed to evaluate possible bladder involvement and assess the functional status of the bladder. A small contracted bladder or vesicular involvement with recurrent tumor may indicate the need for an adjuvant surgical procedure such as salvage cystoprostatectomy and/or urinary diversion.

Salvage surgery after radiotherapy. Salvage surgery is performed after radiotherapy for the purpose of removing all viable cancer cells and thus providing local control as well as systemic cure when possible. The selection of men who may benefit from salvage surgery is done with guidelines similar to those used to select men who are candidates for radical prostatectomy at the time of initial diagnosis. The most appropriate candidates should have had presumed clinically organ-confined disease at the time of radiation without obvious radiographic or DRE evidence of extension outside the prostate since that time. The type of procedure performed depends on the extent of recurrent tumor. Radical prostatectomy is the procedure of choice when the tumor is still believed to be organ-confined, but an anterior or total pelvic exenteration may be necessary in men believed to have extraprostatic involvement.

Cause-specific survival rates for these salvage procedures are reported to be in the range of 60% to 95% at 5 years and 40% to 87% at 10 years.[61-68] Prostatectomy Gleason score, DNA ploidy, and serum PSA appear to be highly predictive of eventual outcome (Table 4).[69,70] The importance of appropriate patient selection is underscored by the series from the Mayo Clinic, where men undergoing salvage radical prostatectomy had a 10-year cancer-specific survival rate of 72%.[67] Almost 40% of these men had organ-confined disease. The cancer-specific survival of men undergoing salvage radical prostatectomy was significantly better than that seen in men with more extensive extraprostatic disease requiring either anterior or total exenteration, where organ-confined disease was found only 16% and 0% of the time.

The potential benefit of salvage surgery should be weighed against a higher incidence of surgical complications.[61-68] Due to the loss of the normal anatomic planes as a consequence of radiation, the surgeon performing salvage surgery should be experienced in performing a difficult dissection with the potential for troublesome bleeding as well as a higher incidence of possible rectal injury. These men suffer from prolonged anastomotic leakage and a higher rate of both incontinence and bladder neck contracture. Reported rates of severe urinary incontinence range from 20% to 64%. Erectile dysfunction is almost universal due to the usual wide excision of the neuro-vascular bundles.

Cryoablation. Cryoablation offers a less invasive therapeutic modality for men with recurrence after radiation therapy. Although initially associated with severe complications when performed via an open perineal approach, technical developments in the area of transrectal ultrasonography, urethral warming devices, as well as superior instrumentation have enabled cryoablation to develop into a safer procedure with potential benefit in some instances. Any long-term benefits of cryoablation in regards to cancer-specific survival have not been reported at this time. The majority of reported series include a small number of men without extended follow-up.[71-74]

One of the largest salvage cryoablation series reports on the use of this technique in 110 men after radiation failure. Almost all of the men did experience a decline in PSA level (96%) and 37% (40/108 men) actually achieved an undetectable PSA level. The majority of men who did not experience a decline in PSA to

Main Points

- After radical prostatectomy, serum prostate-specific antigen should decline to undetectable levels within four to six weeks following surgery.
- Up to 10 years after radical prostatectomy, 30% to 50% of men have disease recurrence, shown by a rising PSA level without other clinical signs.
- Radiation therapy does not eradicate all PSA-producing cells, so persistence of detectable PSA need not imply residual cancer.
- Recurrent cancer that is confined to the prostate has the best chance of long-term cure.
- Androgen ablation may be the most appropriate therapy for the majority of men with recurrence after radiation therapy.

an undetectable level had a subsequent PSA increase from the nadir level. With median follow-up of 11.7 months, only 4 of the 40 men with an undetectable PSA have subsequently experienced an increase in the PSA level.[75]

The incontinence rates in this series were similar to those seen in men undergoing salvage radical prostatectomy, with only 27% of these men with total urinary control. A recent report of the Columbia experience with salvage cryotherapy reported much better preservation of continence, with only 9% of men requiring pads after the procedure.[71] Other reported complications of salvage cryotherapy include erectile dysfunction, perineal pain, urinary obstruction, prostatic abscess, and fistula formation. An update of the quality of life in the patients from the Pisters and colleagues series did not demonstrate any advantage to salvage cryotherapy compared to salvage prostatectomy.[76] Salvage prostate brachytherapy has been used in the past with significant complications and without altering disease progression.[77,78] Lower complication rates and improved response rates were recently reported in a series of 49 men with failure after radiation therapy.[79]

Androgen ablation. Androgen ablation may be the most appropriate therapy for the majority of men with recurrence after radiation therapy, because most men are not candidates for the above-mentioned salvage procedures. The benefits of androgen ablation have not been studied in a randomized, prospective fashion. Schelhammer and associates reviewed their experience with androgen ablation in the treatment of 55 men with clinical local failure after external beam radiation therapy. Cancer-specific median survival was 70 months, and there was no difference between early and delayed hormonal therapy in regard to cancer-specific survival.[80] As is the case in men with failure after radical prostatectomy, the timing of the initiation of hormonal therapy is controversial. As previously discussed, an EORTC trial comparing immediate versus delayed hormonal therapy after failure of definitive local therapy is ongoing.

Radiation Therapy: Conclusions and Recommendations

Unfortunately, the majority of men with a rising PSA above their nadir value after radiation therapy are not candidates for a local salvage procedure. Physical examination is more difficult based upon postradiation fibrosis, and the presence of residual disease in the prostate should be evaluated with ultrasound and prostate rebiopsy in those men who are potential candidates for a salvage procedure. Cross-sectional imaging is needed to decide if residual disease is clinically confined to the prostate or whether local progression has occurred. Cystoscopy should be performed to evaluate for possible bladder neck involvement. Metastatic disease should be ruled out using chest radiographs, radionuclide bone scan, and additional pelvic or abdominal imaging as indicated.

Men without metastatic disease and extensive regional local extension may be candidates for a salvage procedure. Recurrent cancer that is confined to the prostate has the best chance of long-term cure. Overall, these procedures are marked by significant potential morbidity. They are most appropriate for younger, otherwise healthy men who are willing to accept the increased risk in the hope of eventual cure. ■

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